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Osteonecrosis in Children Treated for Acute Lymphoblastic Leukemia: A Magnetic Resonance Imaging Study After Treatment

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The purpose of the study was to find out the prevalence of osteonecrosis in children with acute lymphoblastic leukemia (ALL) in complete bone marrow remission at the end of the treatment. Twenty-eight children with ALL underwent MRI of the upper and/or lower extremities. Bone marrow signal intensity was analyzed on T1-weighted images, where circumscribed lesions with a rim of low signal intensity were considered typical of osteonecrosis. Osteonecrosis was found in 9 of the 28 children (32%, 95% CI 16% to 52%). Five of them were asymptomatic. They had been treated with high risk and intermediate risk protocols, both of which include a delayed intensification phase with dexamethasone. None of the patients with standard risk ALL were found to have developed osteonecrosis. Osteonecroses occurred unexpectedly in symptomless patients and in patients with mild transient symptoms treated with high risk and intermediate risk protocols. Our study suggests that the intensification phase of the treatment protocols with intensive dexamethasone medication might be responsible for the development of osteonecrosis. Med. Pediatr. Oncol. 29:260–265, 1997.

Key words: acute lymphoblastic leukemia; osteonecrosis; magnetic resonance imaging; children; chemotherapy

INTRODUCTION: OSTEONECROSIS COMPLICATES TREATMENT OF ALL

Osteonecrosis, i.e., avascular/necrosis of bone, is known to occur in a variety of conditions [1]. It may complicate the treatment of childhood acute lymphoblastic leukemia (ALL) [2–11]. Little is known about the frequency of osteonecrosis, and its causal factors have not been established, although corticosteroids have been mentioned as the main cause. Osteonecrosis has been reported mainly in symptomatic patients 2 months to 11 years after the beginning of therapy [2–11]. In order to assess the occurrence of osteonecrosis and to find out whether it also occurs in clinically asymptomatic patients in complete bone marrow remission, we undertook a magnetic resonance imaging (MRI) study of children with ALL at the end of their treatment.

MATERIALS AND METHODS

Twenty-eight consecutive children who had been treated for ALL at the Department of Pediatrics, Oulu University, and who were at the cessation of the therapy underwent MR scanning of the extremities during May 1992–April 1996. The time median from the last treatment to the MR examination was 0.06 months (range 0–6 months). There were 15 boys and 13 girls with an age median of 8.5 years (range 3.8–15.5 years), and they were in complete bone marrow remission at the time of the examination. Twenty-five patients had completed their initial treatment for ALL, whereas two patients had been treated for their first relapse and one patient for her second relapse.

The treatment protocols were divided into three risk groups on the basis of the criteria used in all the Nordic countries [12]: standard risk (SR), intermediate risk (IR), and high risk (HR). All the regimens included 4–5 weeks of prednisone at a dose of 60 mg/m2 per day in the induction phase and six weekly injections of vincristine, doxorubisin, and five intrathecal injections of methotrexate. In the SR protocol that is used in the Nordic countries (SR NOPHO) [12,13], the later intensification and central nervous system (CNS) therapies were performed with L-asparaginase, three pulses of intravenous methotrexate infusion and three intrathecal doses of methotrexate, both at 3-week intervals. The IR and HR patients were treated according to ALL-BFM 83 protocols as such or with minor modifications (IR NOPHO and HR NOPHO) [14]. All the IR and HR protocols included an intensification phase early in the treatment with cyclophosphamide, cytosine arabinoside, and oral 6-mercap-

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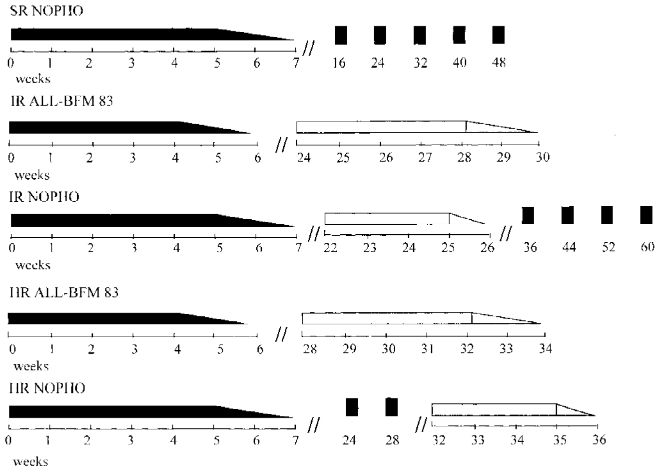

Fig. 1. Schematic presentation of the timing and doses of corticosteroids in the different treatment protocols. SR = standard risk, IR = intermediate risk, HR = high risk. ■ = Prednisone 60 mg/m2/day, ▩ = Dexamethasone 10 mg/m2/day.

topurine, and also teniposide for the HR patients, in addition to the therapy administered to the SR patients. The later intensification and CNS therapies were accomplished with four pulses of intravenous methotrexate and intrathecal methotrexate, both at 2-week intervals. Cranial irradiation was administered to the IR and HR patients as part of the CNS treatment. The IR and HR protocols also comprised a delayed intensification phase, with dexamethasone 10 mg/m2/day for 3–4 weeks following 1 week's taper. The subsequent therapy included oral methotrexate and 6-mercaptopurine for all patients. During the maintenance phase, the SR and IR protocols included 7-day prednisone pulses at a dose of 60 mg/m2 per day repeated every second month for a 1-year period. Seven of the patients with initial treatment were treated with SR NOPHO, four with IR ALL-BFM 83, three with IR NOPHO, two with HR ALL-BFM 83, and nine with HR NOPHO protocols. The patients with relapse had been treated with the SR NOPHO and HR NOPHO protocols. The different corticosteroid treatment schemes in the treatment protocols are presented in Figure 1.

The investigation was carried out according to the provisions of the Declaration of Helsinki, and it had been approved by the Ethical Committee of the Medical Faculty, University of Oulu. Informed consent was obtained from the patients and/or their parents.

The MR examinations were done using a 1.0-T superconducting scanner (Magnetom, Siemens, Erlangen, Germany). In 19 patients, coronal T1-weighted (repetition time [TR], 500 ms; echo time [TE], 15 ms) spin-echo images were obtained from the lower extremities. Nine patients had both the lower and the upper extremities scanned, the upper extremities with T1-weighted images in the sagittal plane. Bone marrow signal intensity was analyzed visually. The radiologists were blinded with regard to the treatment protocols and the patients' symptoms. The images were reviewed and analyzed in consensus by two radiologists. Circumscribed lesions with a rim of low signal intensity among the normally high-intensity marrow on T1-weighted images were considered typical of osteonecrosis [15]. Low-intensity lesions with no typical rim were called patchy [16]. The medical records were reviewed with special attention to the patients' clinical course and possible symptoms of osteonecrosis. The statistical analysis was performed using the

Fig. 2. A 15-year-old girl with a second ALL relapse had mild pains in her right knee. T1-weighted coronal MRI (1.0T, SE 695/15) shows multiple circumscribed lesions with a low-intensity rim in the femoral metapysis and epiphysis and the tibial epiphysis.

TABLE I. Prevalence of Osteonecrosis in Children With ALL at the End of Treatment in Different Treatment Groups

	Primary therapy		Relapse
Osteonecrosis	SR[a]	IR/HR[b]	HR[c]
Yes	0	6	3
No	7	12	0
Total	7	18	3

[a]Standard risk.
[b]Intermediate risk/high risk.
[c]High risk.

TABLE II. Characteristics of Nine Pediatric Patients With ALL Who Developed Osteonecrosis

Patient no:	Sex[a]	Age at diagnosis of primary disease (years)	Risk groups[b]/ initial treatment (I), relapse (R)	Presenting symptoms	Localization of osteonecrosis
1	M	10.0	IR/I	—	both proximal femurs and proximal tibias
2	F	6.4	SR/I HR/R HR/R	mild right and left knee pain, right ankle pain	both femoral heads, proximal femurs and femoral condyles, right tibial condyle, both proximal tibias, both taluses, right calcaneus, naviculare, os cuneiforme med., lat. and intermed. and 5th metatarsal bone, both humeral heads and condyles
3	F	1.6	SR/I HR/R	—	both femoral necks, both distal femurs
4	M	8.3	HR/I	left hip pain	left femoral head
5	F	5.0	HR/I HR/R	mild right knee pain	both distal femurs, left femoral condyle, both proximal tibias
6	F	3.6	IR/I	—	right distal femur and epiphysis, left proximal and distal femur, both taluses
7	M	12.8	HR/I	—	right proximal tibia, left femoral neck
8	F	8.8	HR/I	—	right distal femur
9	F	8.6	HR/I	mild left knee pain	right distal femur and epiphysis, left proximal femur

[a]M = male, F = female.
[b]IR = intermediate risk, SR = standard risk, HR = high risk.

χ^2 test or Fisher's exact test. The precise 95% confidence interval (CI) was computed by the CIA software [17].

In this MRI study, the patients were not systematically radiographed. Some of the patients presenting symptoms (see Table II) were radiographed and a few of the asymptomatic patients with osteonecrosis were radiographed the MRI findings.

RESULTS

Circumscribed lesions with a low-intensity rim consistent with osteonecrosis (Fig. 2) were found in 9 of the 28 children (32%, the 95% confidence interval 16% to 52%). The prevalence of osteonecrosis in the different treatment groups is presented in Table I. Seven of the patients with osteonecrosis had been treated with a HR protocol and two with an IR protocol, both of which included a delayed intensification with dexamethasone and chemotherapy. All three patients who had been treated for ALL relapse developed osteonecrosis, whereas none of the seven patients with SR ALL had evidence of osteonecrosis. There was significant difference between the occurrence of osteonecrosis in the IR/HR patients and the SR patients that was supported by the statistical analysis ($P = 0.04$). No association was found between age at primary diagnosis of ALL, sex, or initial leukocyte count and osteonecrosis. The patient characteristics of those affected are presented in detail in Table II.

Five asymptomatic patients (1, 3, 6, 7, and 8) had osteonecrotic lesions on the MR examination (Fig. 3a,b). Three patients with osteonecrosis had mild transient bone pains during the treatment (patients 2, 5, and 9). Patient 2 had multiple lesions in both the upper and the lower extremities, but had had only a mild short pain episode affecting the knees and the right ankle. In patient 5, MRI revealed osteonecrosis affecting the epiphyseal plate of the proximal tibia and the other multiple lesions. Patient 4 with femoral head osteonecrosis developed hip pains 6 months after the cessation of the therapy.

Patchy marrow lesions (Fig. 4) were detected in seven patients, four of whom had received HR treatment, one IR, and two SR treatment for their primary disease. One patient had a local area of decreased signal intensity in the metaphyseal tibia representing sclerosis due to a healed primary leukemic process. Twelve patients had a normal marrow appearance.

A follow-up MRI examination was performed on 3/9 of these patients 6–18 months after the cessation of therapy. The scan of patient 3 showed regression of the lesions (Fig. 3c), whereas the scan of patient 5 was unchanged. In patient 4, MRI showed progression in his left caput necrosis and the patient underwent a core decompression operation.

DISCUSSION

Osteonecrosis was found in 32% (9 of 28) of our patients at the end of the treatment for ALL, which is

Fig. 3. **(a)** Typical bilateral circumscribed osteonecrotic lesions of the distal femurs on a coronal T1-weighted image (1.0 T, SE 500/15) in an 8-year-old girl with ALL at the end of the treatment. **(b)** Right femur radiographs at the end of the treatment show circumscribed decalcification with a sclerotic rim. **(c)** Fifteen months after the cessation of the therapy, T1-weighted coronal MRI (1.0 T, SE 500/15) shows regression of the lesions.

more than the previously reported 1–17% in symptomatic patients during remission [2,5,6,9]. The confidence interval for our figures was wide, however, indicating that the difference between our results and those of many others was well within random error. In our series, osteonecroses occurred unexpectedly both in completely symptomless patients and in patients with mild transient symptoms.

In addition to the typical circumscribed lesions consistent with osteonecrosis, patchy bone marrow lesions were found in seven patients (25%). Without biopsy, the precise etiology of the patchy lesions remains unclear. They may represent fibrosis or sclerosis due to a healed leukemic process. The long cytostatic therapy seems to cause inhomogeneities with areas of low signal intensity and a patchy pattern, especially in the metaphases [16]. Solitary low-intensity areas could represent bony islands, which should be confirmed by plain films. Some of them also might be small areas of osteonecrosis without the typical circumscribed rim.

Fig. 4. T1-weighted coronal MRI (1.0 T, SE 500/15) illustrates bilateral diffuse, patchy foci of reduced signal intensity in the tibias in a 14-year-old boy with ALL at the end of the treatment.

In the early diagnosis of osteonecrosis, MR has proven to be sensitive and of great value compared with the other imaging methods [2,4,18]. We chose the T1-weighted spin-echo sequence as the screening method for bone marrow pathology. In children, bone marrow signal intensities and relaxation times begin to resemble fat by the age of a few years [19]. Constant circumscribed areas of low signal intensity are assumed to represent areas of osteonecrosis, as shown by biopsy [2]. In addition to having circumscribed lesions, the bone marrow of leukemic children may harbor several other kinds of pathology in MR studies. In untreated patients, the signal intensity of bone marrow is reduced in T1-weighted images due to diffuse leukemic infiltration [19]. When remission is achieved, the intensity of bone marrow returns to normal and the detection of low-intensity rims typical of osteonecrosis becomes possible.

The etiology of osteonecrosis remains unknown. Pathophysiologically, bone death occurs as a result of an imbalance between the metabolic requirements of the osteocyte and the ability of the circulation to meet those needs rather than as a result of a sudden occlusion or functional defect of the blood vessels [20]. There are several conditions associated with the development of avascular necrosis, such as bone trauma, sickle cell anemia, alcohol abuse, occlusive vascular disease, osteomyelitis, radiation, and Gaucher's disease [1]. There are findings of osteonecrosis in patients with untreated malignant disease, including patients with leukemia [21]. The etiology in these cases is thought to be ischemia due to tumour embolization, vessel compression, intravascular coagulation, or toxic chemicals released by tumor cells into the marrow [22].

Most of the reports on children with malignancies and osteonecroses suggest corticosteroids to be the main pathogenetic factor for osteonecrosis [2–11]. There are various hypotheses concerning the pathogenesis of steroid-induced osteonecrosis, including theories of osteoporosis with stress-induced fractures of bone, changes in blood coagulation, vasculitis, and nontraumatic systemic fat embolism [23–25]. The cumulative dose of steroids prior to the onset of osteonecrosis is highly variable [25]. All of our patients with osteonecroses had been treated with IR or HR protocols, which include a delayed intensification phase with intensive dexamethasone medication, whereas no typical osteonecroses were found in the SR patients, who had not received dexamethasone. This suggests that dexamethasone may be responsible for the development of osteonecrosis. However, the role of the other cytostatic drugs cannot be excluded, and there are already a few reports on cases where osteonecrosis has developed in relation to chemotherapy protocols not containing steroids. The authors of these reports have considered the effects of cyclophosphamide, 5-fluorourasile, vinblastine, and bleomycin [26–30]. Patients who have undergone several ALL treatments because of relapses seem to have an increased risk for osteonecroses. In this study all of the three patients who had been treated for ALL relapse developed osteonecrosis.

Three of the nine children with osteonecrosis underwent follow-up MR scans of the lesions. One of the patients had progression in the lesion, which led to an operation. One of them had regression of the osteonecroses in a control scan 13 months after the diagnosis of the lesions. The MR finding was unchanged in the third patient 18 months after the first examination. This gives rise to the question of what the prognosis of these osteonecroses will be in the future and how much disability they will cause to these children in the long run. It is evident that this problem requires further consideration and follow-up studies.

CONCLUSION

Osteonecroses occur in symptomless patients and in patients with mild transient symptoms treated with high risk and intermediate risk protocols. The intensification phase of the treatment protocols with intensive dexamethasone medication might be responsible for the development of osteonecrosis.

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